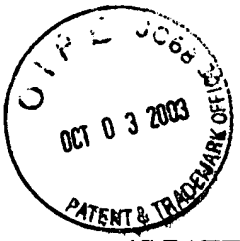

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: David M. GOLDENBERG *et al.*

Title: IMMUNOTHERAPY OF AUTOIMMUNE DISORDERS USING ANTI-CD22 ANTIBODIES

Appl. No.: 09/590,284

Filing Date: 06/09/2000

Examiner: J. Roark

Art Unit: 1644

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Hans J. Hansen declare that:

1. I am a citizen of the United States, residing at 6014 Angler Drive, Picayune, MS 39466. I was formerly Vice President of Research and Development at Immunomedics, and I remain a Vice President and advisor to the company. A copy of my Curriculum Vitae is appended hereto as Exhibit A.

2. I have reviewed the Official Action dated April 4, 2003, and the Advisory Action dated September 16, 2003, as well as the references cited in these communications.

3. The primary reference cited in this application is Aruffo. Aruffo deals with an autoimmune therapy that is totally unrelated to those cited in the other documents, as detailed below. For a variety of reasons, a skilled artisan would not have attempted to combine the teaching of Aruffo with the approaches set forth in the other cited documents at the time the presently claimed invention was filed, but even if all the references were combined, the presently claimed invention would still not result.

4. In the first place, Aruffo relates to a completely different mechanism for attacking autoimmune disease. Aruffo's invention relates to a blocking of the interaction between CD40 and its cognate ligand, gp39. The interaction between CD40 and gp39 "primes B cells to respond to subsequent stimulatory signals leading to B cell proliferation, differentiation and isotype switching" (Kiener *et al.*, *J. Immunol.* (1995)) and relates to "T cell-dependent B cell activation" (Foy *et al.*, *J. Exp. Med* (1993)). See also, product information for anti-mouse CD154 ("gp39 is expressed transiently by activated T cells...gp39 interaction with CD40 transduces signals for T-dependent B-cell activation" -- http://www.ebioscience.com/ebioscience/specs/antibody_16/16-1541. An antibody to CD19, CD20 or CD22 would not prevent interaction between CD40 and gp39, the function of the Aruffo antibody, and thus a person of skill in the art would have had no reason to substitute one of these antibodies for the Aruffo anti-CD40 antibody.

5. The rejection cites portions of Aruffo that suggest that B cells are ***transiently*** depleted when the anti-CD40 antibody is administered. However, column 9, lines 45-46 clearly states that "[r]ecovery of B cells to normal levels occurred within 2-3 weeks post-treatment." More importantly, Figure 3 of Aruffo shows that a sustained suppression of the host's antibody response occurred beyond 3 weeks when B cells had returned to normal levels. This would not have motivated the use of B-cell antibodies in the treatment of autoimmune disease. To the contrary, a person of ordinary skill would have concluded in line with Aruffo's teaching that the B-cell depletion is an undesirable side effect that should be minimized rather than enhanced.

6. As noted above, the result sought by Aruffo is a blocking of the interaction between CD40 and gp39 ("a key functional property for the desired anti-CD40 mAb was the capacity to completely block the interaction of CD40 and its ligand, gp39" – column 7, lines

21-24), leading to significant suppression of antibody response. To this end, Aruffo utilized various assay formats to select antibody candidates for further testing. From ***200*** initial candidates (column 7, lines 19-20), the field was limited to two for testing *in vivo* (column 8, lines 50-53). While both of these produced a transient reduction in peripheral B cell levels, ***only one of them, 2.220, significantly suppressed antibody response.*** The other candidate, 2.36 did not meet Aruffo's purpose. The clear message to be taken from Aruffo is that the ability to block interaction between CD40 and gp39 is a necessary, but not sufficient, basis for success in the ability to suppress antibody response and hence serve as a therapy in autoimmune diseases. Given this teaching in Aruffo, a skilled artisan would not have been motivated to substitute an antibody to CD19, CD20 or CD22 for the anti-CD40 antibody of Aruffo.

7. Yet another difference between the presently claimed invention and Aruffo is the fact anti-CD40 antibody targets an antigen also found on thrombocytes. See *Circ. Res.*, 2003 May 16;92(9):944-6, stating that "CD40 is constitutively expressed on platelets and provides a novel mechanism for platelet activation". Targeting other cells like thrombocytes could cause adverse events. By contrast, tests utilizing CD20 and CD22 antibodies of the presently claimed invention have not revealed any thrombocyte-associated adverse events. Similarly, I am not aware of any reports that CD19 is linked to thrombocytes, and therefore, would not expect antibodies to CD19 to be associated with adverse thrombocyte events. See *J Immunol.*, 1987 May 1;138(9):2793-9, stating that CD19 is "the broadest lineage specific surface marker for B cells: it is present on the surface of virtually all B lymphocytes, including early B progenitor cells." This underscores just one of the basic differences between the present approach and that of Aruffo.

8. Tedder is cited as a secondary reference in the rejection based on Aruffo. As discussed above, Tedder and Aruffo take entirely different approaches to the treatment of autoimmune disease, and for this reason alone a skilled artisan would not have been motivated to substitute an antibody from Tedder for an anti-CD40 antibody of Aruffo for autoimmune therapy. Further, even if they were combined, Tedder does not remedy Aruffo's deficiencies because it only teaches use of CD22 antibodies that "block CD22 adhesive function". In column 4, lines 32-35, Tedder clearly states that "[t]he present invention concerns a series of novel monoclonal antibodies (mAb), designated HB22, that specifically block cell adhesion to CD22." This is directly contrary to Aruffo's approach of blocking the interaction between CD40 and gp39.

9. If Tedder were combined with Aruffo, the result would be a combination of an anti-CD40 antibody and an anti-CD22 antibody which does not bind to the A, B, D, or E epitopes of CD22. As shown in Table III of Tedder (col. 11), the antibodies of Tedder's invention do not bind to the A, B, C, D, or E epitopes of CD22. This is more clearly stated in column 10, lines 64-67, where Tedder observes that "the region of CD22 that mediates ligand binding may be located in close proximity to a region overlapping epitopes B, C, and D." This teaches directly away from use of CD22 antibodies as presently claimed. In other words, Tedder's results show that Tedder's antibodies are distinct from antibodies of the prior art targeting the B, C, and D epitopes and that this is functionally a critical difference for Tedder's stated purpose because Tedder only utilizes antibodies that block cell adhesion to CD22. In sum, Tedder's entire patent is focused on identifying antibodies that target a new epitope of CD22 that is not the same as the A, B, C, D, or E epitope, but rather forms a distinct epitope that is near B, C, and D (and may overlap them) and that is responsible for blocking cell adhesion to CD22, a function alleged by Tedder not to be obtained by the prior

art antibodies. Thus, I would not have been motivated based on Tedder to select an antibody targeting the A, B, D, or E epitope of CD22 for use in autoimmune therapy.

****

I hereby declare that all the statements made herein of my known knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Oct 2, 2003
Date

Hans J. Hansen, PhD.

Exhibit A.

Curriculum Vitae of Dr. Hans Hansen

CURRICULUM VITAE

HANS JOHN HANSEN

EDUCATION:

B.S. Wisconsin State College 1955.
Ph.D. Tulane University, Dept. of Biochemistry, School Med., 1960.

EMPLOYMENT:

Research Fellow, Touro Research Institute, 1990-1963.
Research Associate, Touro Research Institute, 1963-1965
Principal Investigator, Touro Research Institute, 1966-1969.
Group Chief, Central Research, Hoffmann-LaRoche, 1971-1973.
Director Immunology, Central Research, Hoffmann-LaRoche, 1974-1982.
Group Director, Research, Ortho Diagnostic Systems Inc., 1982-1985.
Director Cell Biology, Immunomedics Inc., 1985-1987.
Vice President Exploratory Research, Immunomedics Inc., 1987-1992.
Vice President R & D, Immunomedics Inc., 1992-present.

ACADEMIC APPOINTMENTS:

Assist. Prof., Tulane Medical Sch., Dept Biochem., 1960-1963.
Assoc. Prof., Tulane Medical Sch., Dept Biochem., 1963-1970.
Assoc. Prof., Tulane Medical Sch., Dept. Med., 1967-1969.
Assoc. Prof., Tulane School of Public Health, 1968-1970.
Adjunct Member, Garden State Cancer Center, 1990-present.

PROFESSIONAL SOCIETIES:

American Association of Immunologists.
American Association for Cancer Research.
Society of Nuclear Medicine.
American Society for Clinical Nutrition (former member).
American Institute of Nutrition (former member).
New York Academy of Sciences (former member).
Sigma Xi (Life member).

OTHER ACADEMIC:

Supervisor of seven Ph.D. Dissertations.
Supervisor of eight M.S. Dissertations.
Member, NCI Development Therapeutics Committee, 1975.
Member, NCI Tumor Markers Working Group, 1977.
Member, NCCLS Alpha-fetoprotein Subcommittee, 1980.
Member, NCI National Prostatic Cancer Project Group, 1980.

HANS J. HANSEN PATENTS

1. Title: Antigens:
   Number: U.S. 3,697,638
   Issued: October 10, 1972
   Inventor: Hans John Hansen

   Assignee: Hoffman-La Roche Inc., Nutley, N.J.

2. Title: Localization of Tumors by Radiolabeled Antibodies.
   Number: U.S. 3,927,193
   Issued: December 16, 1975
   Inventors: Hans John Hansen
   Frederick James Primus

   Assignee: Hoffman-La Roche Inc., Nutley, N.J; Immunomedics, Inc.

3. Title: Carcinoembryonic Antigens
   Number: U.S. 3,867,363
   Issued: February 18, 1975
   Inventors: Hans John Hansen

   Assignee: Hoffman-La Roche Inc., Nutley, N.J.

4. Title: Radioimmunoassay for Insulin
   Number: U.S. 3,867,518
   Issued: February 18, 1975
   Inventors: John William Coffey
   Hans John Hansen

   Assignee: Hoffman-La Roche Inc., Nutley, N.J.

5. Title: Carcinoembryonic Antigens
   Number: U.S. 3,956,258
   Issued: May 11, 1976
   Inventors: Hans John Hansen

   Assignee: Hoffman-La Roche Inc., Nutley, N.J.

6. Title: Carcinoembryonic Antigens
   Number: U.S. 4,180,499
   Issued: December 25, 1979
   Inventor: Hans J. Hansen

   Assignee: Hoffman-La Roche Inc., Nutley, N.J.

7. Title: Carcinoembryonic Antigen Determination
   Number: U.S. 4,299,815
   Issued November 10, 1981
   Inventor: Hans J. Hansen
   Alfred D. Myl
   Jacques P. Vandevoorde

   Assignee: Hoffman-La Roche Inc., Nutley, N.J.

HANS J. HANSEN PATENTS (continued)

8. Title: Method for Radiolabeling Antibody Fragments
   Number: U.S. 5,061,641
   Issued: April 1, 1988
   Inventors: Dan Shochat
   Hans J. Hansen
   Robert S. Wu

   Assignee: Immunomedics, Inc.

9. Title: CEA Immunoassay Free of Human Anti-Mouse Antibody False Positives
   Number: U.S. 4,900,684
   Issued: February 13, 1990
   Inventor Hans J. Hansen

   Assignee: Immunomedics, Inc.

10. Title: Detection and Treatment of Infectious and Inflammatory Lesions
    Number: U.S. 4,925,648
    Issued: May 15, 1990
    Inventor: Hans J. Hansen
    Milton D. Goldenberg

    Assignee: Immunomedics, Inc.

11. Title: Preparation and Use of Immunoconjugates
    Number: U.S. 5,443,953
    Issued: August 22, 1995
    Inventors: Hans J. Hansen
    Shui-on Leung
    Jerry Shevitz

    Assignee: Immunomedics, Inc.

12. Title Methods for Technetium/Rhenium Labeling of Proteins
    Number: U.S. 5,328,679
    Issued: July 12, 1994
    Inventor: Hans J. Hansen
    Gary L. Griffiths
    Anastasia Lentine-Jones

    Assignee: Immunomedics, Inc.

13. Title: Methods for Radiolabeling Antibody Fragments
    Number: U.S. 5,514,363
    Issued: May 7, 1996
    Inventor: Dan Shochat
    Hans J. Hansen
    Robert S. Wu

    Assignee: Immunomedics, Inc.

HANS J.HANSEN PATENTS (continued)

14. Title: Therapy Conjugates of Toxins and Drugs
Number: U.S.5,541,296
Issued: July 30, 1996
Inventor: Hans J. Hansen, Gary L. Griffith, Anastasia Lentine-Jones, David M. Goldenberg.
Assignee: Immunomedics, Inc.

15. Title: Conjugates of Antibodies and Bifunctional Ligands.
Number: U.S. 5,612,016.
Issued: March 18, 1997.
Inventor: Gary L. Griffiths, Habibe Diril, Hans J Hansen.
Assignee: Immunomedics, Inc.

16. Title: Preparation and Use of Immunoconjugates.
Number: U.S. 5,635,603.
Issued: June 3, 1997.
Inventor: Hans J. Hansen, Shui-on Leung, Jerry Shevitz, Gary L. Griffiths, Seregulam V. Govindan
Assignee: Immunomedics, Inc.

17. Title: Therapeutic Conjugates of toxins and Drugs.
Number: U.S. 5,601,825.
Issued: February 11, 1997.
Inventor: Hans J Hansen, Gary L. Griffiths, Anastasia Lentine-Jones, David M. Goldenberg.
Assignee: Immunomedics, Inc.

18. Title: Chimeric Antibody for Detection and Therapy of Infectious and Inflammatory Lesions.
Number: U.S. 5,637,288.
Issued: June 10, 1997.
Inventor: David M. Goldenberg, Hans J. Hansen.
Assignee: Immunomedics, Inc.

19. Title: Modified Radioantibody Fragments for Reduced Renal Uptake.
Number: U.S. 5,670,132.
Issued: September 23, 1997.
Inventor: Gary L. Griffiths, Hans J Hansen, Habibe Karacay.
Assignee: Immunomedics, Inc.

20. Title: Chimeric Antibody for Detection and Therapy of Infectious and Inflammatory Lesions.
Number: U.S. 5,677,427.
Issued: October 14, 1997.
Inventor: David M. Goldenberg, Hans J. Hansen.
Assignee: Immunomedics, Inc.

21. Title: Treatment of Infectious and Inflammatory Lesions
Number: U.S. 5,705,158.
Issued: January 6, 1998.
Inventor: Hans J Hansen, David Milton Goldenberg.
Assignee: Immunomedics, Inc.

HANS J.HANSEN PATENTS (continued)

22. Title: Radioactive Phosphorus Labeling of Proteins for Targeted Radiotherapy.
Number: U.S. 5,728,369.
Issued: March 17, 1998.
Inventor: Gary L. Griffiths, Hans J Hansen, Habibe Karacay.
Assignee: Immunomedics, Inc.

23. Title: Detection and Therapy of Lesions with Biotin/Avidin-metal chelating protein conjugates.
Number U.S. 5,736,119.
Issued: April 7, 1998.
Inventor: David Milton Goldenberg, Gary L. Griffiths, Hans J. Hansen.
Assignee: Immunomedics, Inc.

24. Title: Thiolation of Peptides for Radiouclide-Based Radiodetection and Radiotherapy.
Number: U.S. 5,746,996.
Issued: May 5, 1998.
Inventor: Serengulam V. Govndan, Gary L. Griffiths, Hans J. Hansen.
Assignee: Immunomedics, Inc.

25. Title: Thiolation of Proteins for Radionuclide-Based Radioimmunodetection and Radioimmunotherapy.
Number: U.S. 5,772,981.
Issued: June 30, 1998.
Inventor: Seregulam V. Govendan, Ruth Grebenau, Gary L. Griffiths, Hans J. Hansen.
Assignee: Immunomedics, Inc.

26. Title: Immunoconjugates and Humanized Antibodes Specific for B-Cell Lymphoma and Leukemic cells.
Number: U.S. 5,789,554.
Issued: August 4, 1998.
Inventor: Shui-on Leung, Hans Hansen.
Assignee: Immunomedics, Inc.

27. Title: Multi-Stage Cascade Boosting Vaccine.
Number: U.S. 5,798,100.
Issued: August 25, 1998.
Inventor: Hans J. Hansen.
Assignee: Immunomedics, Inc.

28. Title: Method for Antibody Targeting of Therapeutic Agents.
Number: U.S. 5,851,527.
Issued: December 22, 1998.
Inventor: Hans J Hansen.
Assignee: Immunomedics, Inc.

29. Title: CDR-Grafted Type III Anti-CEA Humanized Mouse Monoclonal Antibodies.
Number: U.S. 5,874,540.
Issued: February 23, 1999.
Inventor: Hans J Hansen, Kathryn L. Armour.